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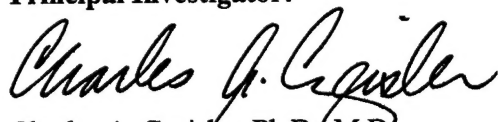
## FINAL REPORT

Submitted on May 18, 2000  
to  
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### CLINICAL TRIAL OF THE EFFECT OF EXERCISE ON RESETTING OF THE ENDOGENOUS CIRCADIAN PACEMAKER

**Grant Number: F49620-97-10246**

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1. Cover Page:

2. Objectives:

The objectives of the research effort *have not changed*; they remain as follows:

Specific Aim 1: test the hypothesis that a 9-hr phase delay shift of the duty-rest schedule, such as that required for either transmeridian travel or night operations, will induce physiologic maladaptation in the endogenous circadian rhythms of core body temperature, plasma melatonin, reaction time, alertness and performance;

Specific Aim 2: test the hypothesis that multiple nightly bouts of exercise will induce significant delays in the endogenous circadian rhythms of core body temperature, plasma melatonin, reaction time, alertness and performance relative to the control group, even in the absence of properly timed exposure to photic cues;

Specific Aim 3: test the hypothesis that exercise-induced phase delay shifts of will facilitate adaptation of these rhythms to an imposed duty-rest schedule, thereby improving sleep efficiency during daytime sleep and improve reaction time, alertness and performance during scheduled waketime at night relative to control group.

3. Status of Effort:

We proposed to study six subjects per year over three years for a total of eighteen research subjects. In the period covering 9/97 -12/99, we impaneled twelve research subjects and data collection has been completed on eleven. The data collected during the 15-day study include: pre-study estimated oxygen uptake capacity, minute-by-minute samples of core-body temperature; hourly blood plasma samples; neurobehavioral testing including the reaction time task (psychomotor vigilance test) every two hours; nightly polysomnographic recordings; daily subjective assessments of sleep quality questionnaires; physiologic data from the 3/night for seven nights exercise/control sessions (monitoring average power, RPM, distance cycled, calories burned, heart rate); and urine samples collected every three waking hours.

4. Accomplishments/New Findings:

In a crossover design, eight healthy young men mean  $\pm$  SD age  $22.67 \pm 4.23$  years underwent a forced desynchrony protocol lasting 44-days. Subjects lived in the laboratory and were maintained in an environment free from time cues. Subjects were scheduled to 3, 24-hr baseline days, then to 48, 20-hr days to simulate rapid transmeridian travel. During the treatment condition, exercise occurred three times each 20-hr day.

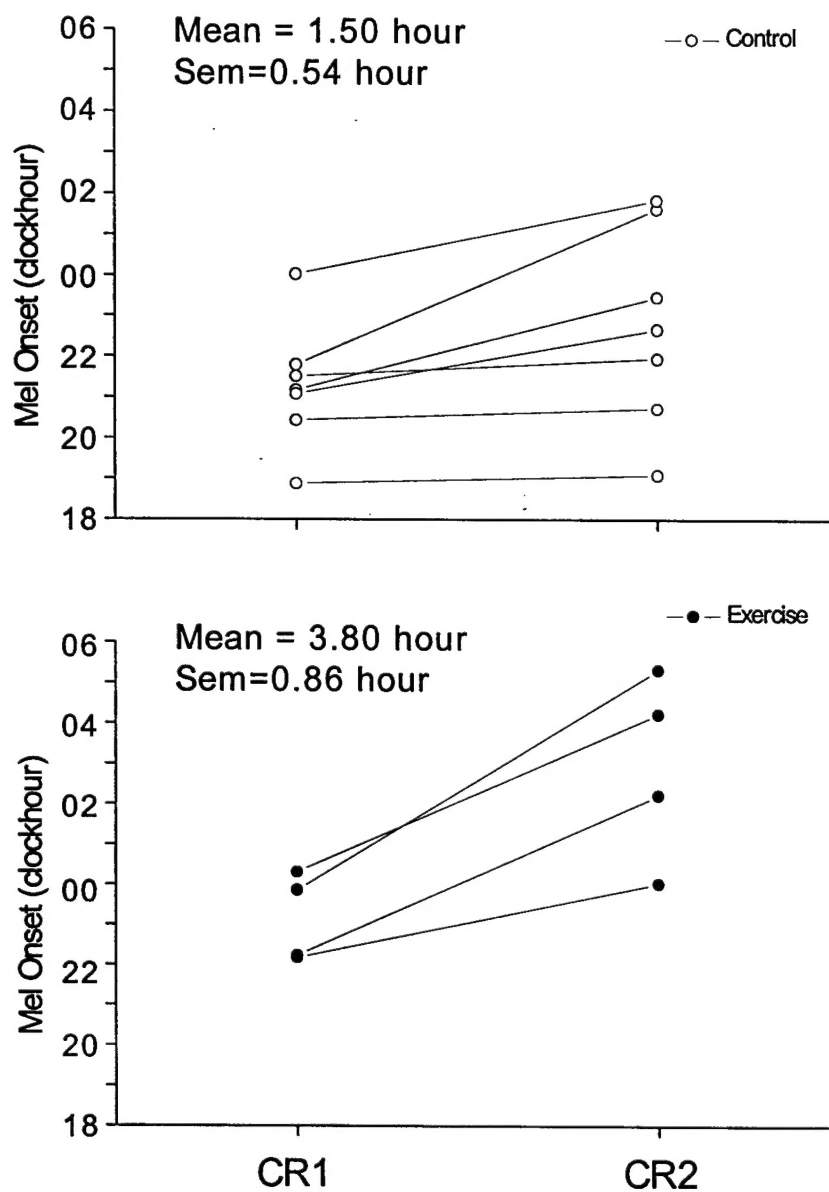
Exercise bouts began: +0.75-hrs, +4.5-hrs. and +8.25-hrs after waketime. Bouts were 45-min long and separated by 3-hr rest intervals. Intensity = ~65% predicted maximal heart rate with RPM=65-70 on a Cybex "The Semi" ergometer. Core body temperature was collected continuously via a rectal temperature sensor. The Psychomotor Vigilance Test, a 10-min reaction time test, was administered every 75-minutes during waketime.

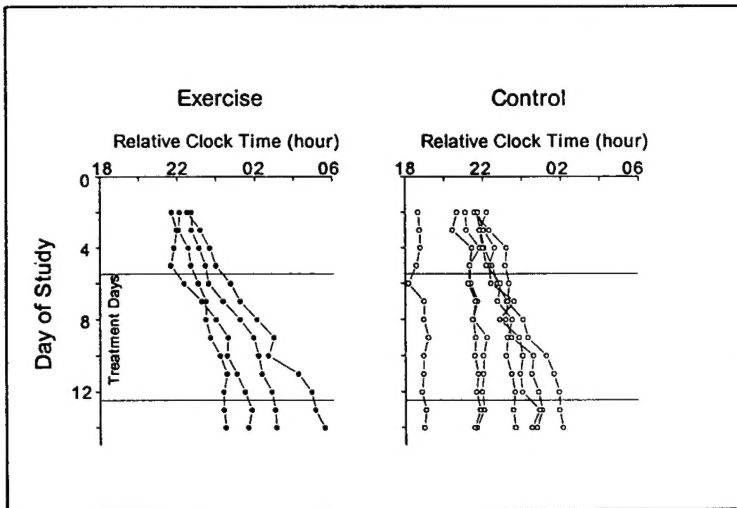
Two-factor repeated measures ANOVA revealed that median reaction time varied significantly as a function of circadian phase ( $F_{7,21}=21.83$   $p<.0001$ ) and prior wakefulness ( $F_{5,15}=5.97$   $p<.003$ ) in both the exercise and control conditions. However, median reaction time was significantly reduced in the exercise condition as a function of these processes ( $F_{1,3}=18.56$   $p<.023$  and  $F_{1,3}=25.65$   $p<.015$  respectively).

These results suggest that moderate intensity exercise can enhance neurobehavioral performance under conditions simulating jet lag, perhaps by enhanced CNS activation. However, the exact mechanism by which exercise affects cognitive functioning has yet to be elucidated.

Results from the analysis of core body temperature data derived from the first 12 studies are encouraging. Data from the pre- and post stimulus constant routines (CR) were assessed to determine whether repetitive, nightly bouts of exercise can elicit significant phase delay shift of the endogenous circadian core body temperature rhythm. We anticipated that over the nine intervening 24-hr-cycles between the pre- and post CR assessments, the endogenous circadian pacemaker of the four subjects studied under the control conditions would drift with an average intrinsic period of ~24.17-hr, which would result in an observed phase delay shift of the endogenous circadian temperature rhythm of ~1.5-2.5-hr. Indeed, analysis of the plasma melatonin onset data from the control condition revealed mean  $\pm$  SEM phase delay shifts of  $1.50 \pm 0.54$ -hr. Examination of the data from the exercise condition reveals a mean  $\pm$  SEM phase shift of  $3.80 \pm 0.86$ -hr in the plasma endogenous melatonin rhythm. Evaluation of significant statistical differences between the active and control conditions awaits completion of the cohort. The nearly two-hour difference in phase adaptation to the protocol suggests that exercise can significantly facilitate circadian adaptation to night shift work and jet lag.

**Figure 1.** Preliminary results for the effects of exercise on circadian adaptation to night shift work / jet-lag





5. Personnel Report:

- |                                     |                              |
|-------------------------------------|------------------------------|
| 1. Charles A. Czeisler, Ph.D., M.D. | Professor of Medicine        |
| 2. Rod J Hughes, Ph.D.              | Instructor of Medicine       |
| 3. Val Saxe                         | Chief Technician             |
| 3. Lisa Bocelli                     | Technical Research Assistant |
| 4. Zachry Zichitella                | Technical Research Assistant |
| 5. Serena Ma                        | Research Assistant           |

6. Publications:

Rimmer DW, Dijk DJ, Wyatt JK, Dinges DF, Czeisler CA. Exercise of moderate intensity can improve visual reaction time. Annual Meeting of the American College of Sports Medicine Annual Meeting, 1998.

Rimmer DW, Czeisler CA. Exercise of moderate intensity does not affect the period of the endogenous circadian pacemaker. *Sleep Research*, 26:749, 1997.

7. Interactions/Transitions:

A. Participation/presentations:

DW Rimmer:

June 1998:

Annual Meeting of the American College of Sports Medicine. Orlando, FL

DJ Dijk/CA Czeisler  
Colorado Springs, CO

B. Consultative and advisory functions:

C. Transitions:

Data from these experiments will be incorporated into a model of alertness and performance currently being developed to counteract fatigue associated with Air Force missions. The model is being developed through the support of the AFOSR Partnership for Research Excellence and Transition Program (PRET), Center on Countermeasures for Jet Lag and Sleep Deprivation organized at the University of Pennsylvania.

8. New discoveries, inventions, or patent disclosures:

None

9. Honors/Awards:

CA Czeisler:

- Plenary Address, Japanese Sleep Research Society, Sapporo, Japan (1996).
- Elected to the Association of American Physicians (1997).
- Keynote Speaker, Associated Professional Sleep Societies Annual Meeting, San Francisco, CA (June 1997).

DW Rimmer:

- Student Investigator Award. New England Chapter Meeting of the American College of Sports Medicine, Providence, RI (September 1997).
- SRS Trainee Travel Award to the Eleventh Meeting of the Association of Professional Sleep Societies (APSS) in San Francisco, CA. (1997).